

6.0: SUMMARY OF ALL RESEARCH FINDINGS

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Altria Client Services LLC (“ALCS”) on behalf of U.S. Smokeless Tobacco Company LLC (“USSTC”)¹ submits this Modified Risk Tobacco Product Application (MRTPA) to market Copenhagen® Snuff Fine Cut² (candidate product) with the following modified risk claim:

“IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer.”

Adult tobacco consumers (ATC), especially those who smoke cigarettes and who cannot, or will not, cease using tobacco products altogether need accurate and non-misleading information about the relative risks of tobacco products so that they can make informed decisions about which products to use. Accurate information about the health risks of moist smokeless tobacco³ (MST) relative to cigarette smoking is all the more necessary because, currently, the vast majority of adult tobacco consumers do not perceive a substantial risk differential between MST and cigarettes (O'Connor, Hyland, Giovino, Fong, & Cummings, 2005; O'Connor et al., 2007; Smith, Curbow, & Stillman, 2007; Tomar & Hatsukami, 2007). The FDA’s Population Assessment of Tobacco and Health (PATH) survey indicates that more than 90 percent of U.S. adults and adult smokers perceive smokeless tobacco (ST) products, including MST, to be as or more harmful than cigarettes.⁴ Additionally, a vast majority of smokers (71%) and dual users (72%) did not believe that ST is less harmful than cigarettes.⁵ To begin to address this discrepancy, we propose a modified risk claim for the candidate product that provides relevant and accurate information specifically regarding lung cancer.

¹ USSTC is a wholly owned subsidiary of Altria Group, Inc. (“Altria”). Altria Client Services LLC provides certain services, including regulatory affairs, research and development, and health sciences to the Altria family of companies. “We” or similar pronouns are used throughout to refer to USSTC.

² Copenhagen® Fine Cut and variants thereof have been on the market since 1822. Since 2007, USSTC has made minor modifications to Copenhagen® Snuff Fine Cut, which are the subject of a separate pending Substantial Equivalence review. The candidate product subject to the MRTPA is the product for which FDA granted grandfathered status (Grandfather Number – GF1200194) on November 1, 2012.

³ Smokeless tobacco (often abbreviated as SLT or ST) products sold in the U.S. typically consist of “moist smokeless tobacco” (abbreviated as MST) sometimes referred to as “moist snuff tobacco,” which consists of cut tobacco leaves (long cut or fine cut) which has significant moisture. “Dry snuff” is a smokeless tobacco made from ground or pulverized tobacco leaves that is inhaled or “snuffed” into the nasal cavity. The published literature does not often distinguish the different types of smokeless tobacco (ST) products sold in the U.S.; therefore, we use the abbreviations as described by the authors in the literature. The candidate product is a moist smokeless tobacco product, abbreviated as MST, where applicable.

⁴ Based on Hyland et al., *Highlighted Findings from the Wave 1 of the Population Assessment of Tobacco and Health Study* presented at the 2016 Annual Meeting of the Society for Research on Nicotine and Tobacco, Chicago, Illinois.

⁵ Based on the 2015 National Cancer Institute Health Information National Trends Survey (HINTS) ([Appendix 2.3.-4](#))

Cigarette smoking is an established preventable risk factor for many cancers. According to CDC estimates, of the more than 480,000 deaths in the U.S. attributable each year to cigarette smoking, 163,700 are cancer related, with 117,700 alone being lung cancer.⁶ In a recent evaluation of tobacco product risk, [Andreotti et al. \(2016\)](#) noted that cigarette smokers have an increased risk of lung cancer that is 15 times greater than people who do not use tobacco. As noted by [Parsons et al. \(2010\)](#), “Prognosis of lung cancer is poor; around 7% of patients survive for five years, and most patients are treated palliatively from diagnosis. The difficulty and discomfort of smoking cessation may mean that many patients with advanced disease choose to continue smoking.” In contrast to cigarette smoking, several large epidemiology studies and our analyses of nationally representative linked mortality data find that the risk of lung cancer among exclusive ST users is much lower than for smokers (further discussed in Section 6.1.2.1.2). Even if we consider some of the published literature reporting higher lung cancer risk in ST users compared to never tobacco use and assume an association between ST use and lung cancer risk, these risk estimates are far lower than those reported for cigarette smoking. The proposed modified risk claim provides accurate and non-misleading information necessary for AS to make informed decisions about switching to the candidate product and presents a meaningful opportunity to impact public health by lowering the incidence of cigarette-related mortality.

There is scientific consensus that non-combustible tobacco products, such as ST products⁷ including the MST product subject of this MRTPA, are lower on the continuum of risk than conventional cigarettes, and that adult smokers who switch from cigarette smoking to exclusive use of non-combustible products like ST would lower their individual health risks ([Hatsukami, Ebbert, et al., 2007](#); [Hatsukami, Joseph, et al., 2007](#); [Zeller & Hatsukami, 2009](#)). Further, FDA Commissioner Dr. Scott Gottlieb recently expressed similar thoughts:

“As we move forward, I also hope that we can all see the potential benefits to addicted cigarette smokers, in a properly regulated marketplace, of products capable of delivering nicotine without having to set tobacco on fire. The prospective benefit may be even greater for the subset of current cigarette smokers who find themselves unable or unwilling to quit.”⁸

We submit this MRTPA as the first step towards providing ATC with relevant information regarding the differential risk between the candidate product and cigarettes so that they can make informed decisions. Section 911(g)(1)(A) of the Federal Food, Drug and Cosmetic Act (FDCA) requires applicants to demonstrate that a candidate product will “significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole.” FDA has identified five key areas of consideration necessary for determining if an applicant meets this standard:

⁶ https://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/index.htm

⁷ Statement refers to smokeless tobacco product types commonly used in the United States and may not apply to various smokeless tobacco types traditionally used in other parts of the world, particularly Asia and Africa.

⁸ Remarks by Scott Gottlieb, M.D., Commissioner of Food and Drug Administration, July 28, 2017, White Oak, MD

1. Health Risks of the Tobacco Product
2. Effect of Marketing on Consumer Understanding and Perceptions
3. Effect on Tobacco Use Behavior Among Current Users
4. Effect on Tobacco Use Behavior Among Nonusers
5. Effect on the Population as a Whole

Our MRTPA presents scientific evidence to inform these five key areas of investigation, including individual health risks and potential population effects. In Sections 6.1 through 6.5, we summarize research findings related to these topics.

1. Health Risks of the Tobacco Product

Section 6.1 discusses the scientific evidence substantiating the proposed modified risk claim by addressing the absolute and relative health risks of the candidate product and possible changes in health risks associated with certain tobacco use behaviors. Within the hierarchy of evidence, we assign significant weight to the epidemiological studies, as they provide health outcomes resulting from long-term product use behavior under real-world conditions. Nonclinical and clinical studies are also important and provide additional information regarding the likelihood of health outcomes and the mechanistic basis for the epidemiological findings. We summarize the current scientific evidence showing the substantial relative difference in lung cancer mortality risk between ST use and cigarette smoking. Additionally, we provide scientific findings regarding all-cause mortality, viewed as a representative end-point for overall smoking-related diseases, and other specific serious and often fatal diseases associated with tobacco use including lung cancer.

- Section 6.1.1 summarizes the data sources and hierarchy of evidence.
- Section 6.1.2 summarizes the health risks of the candidate product as compared to using other tobacco products on the market, including tobacco products within the same class of products.
- Section 6.1.3 summarizes the health risks associated with initiating use of the candidate product as compared to never using tobacco products.
- Section 6.1.4 summarizes the changes in health risks for users who switch from using another tobacco product to using the candidate product, including tobacco products within the same class of products.
- Section 6.1.5 summarizes the health risks associated with using the candidate product in conjunction with other tobacco products.
- Section 6.1.6 summarizes the health risks associated with switching to the candidate product as compared to quitting the use of tobacco products.
- Section 6.1.7 summarizes the health risks associated with switching to the candidate product as compared to using an FDA-approved tobacco-cessation medication.

The candidate product has been marketed in the U.S. since 1822 and comprised a considerable share of the ST product market, and more specifically the MST market, for

many years. Consequently, the substantial body of published scientific evidence describing the health effects of using ST products (in general) in the U.S. reflects the candidate product. In Section 7.4.1, we provide new perspective on the comparative mortality risks of cigarette smoking and ST through analysis of data from current longitudinal U.S. datasets describing the mortality risk from modern ST products, including the candidate product. Additionally, Section 7.5.6-1 and 7.5.6-2 summarizes published epidemiology related to the use of ST in the U.S. and reviews relevant published literature on the health risks of ST products.

Taken together, these data provide a comprehensive evaluation of the health risks of ST use generally, and the candidate product specifically, and substantiate the scientific accuracy of our proposed modified risk claim. The epidemiological evidence provides the ultimate proof that use of ST products presents substantially lower morbidity and mortality risks compared to cigarette smoking, particularly lung cancer. This evidence is further substantiated by conclusions from the nonclinical and clinical evidence.

2. Effect of Marketing on Consumer Understanding and Perceptions

Section 6.2 summarizes the key findings regarding whether adult users and non-users of tobacco products understand the proposed modified risk claim and whether they are misled to believe that the candidate product is without risk.

This section presents results from our Claim Comprehension and Intentions (CCI) Study (Section 7.3.2) evaluating comprehension of the claim and the effect of the claim on risk perceptions among (1) adult tobacco consumers who use MST, cigarettes, or both products; and (2) adult non-users, including never-users of tobacco and former tobacco users. The CCI Study evaluated the proposed claim in the context of the four rotating federally mandated warnings that appear on ST products.

It is widely documented that a large majority of ATC in the U.S. believe that ST products are either as risky as, or more risky than, cigarettes.

- Section 6.2.2 provides an overview of our program for development and testing of the proposed claim.
- Section 6.2.6 summarizes the evidence regarding consumer comprehension of the proposed claim and its significance in the context of one's health.
- Section 6.2.7 summarizes consumer beliefs about the health risks of using the product relative to other tobacco products, including those within the same class of products.
- Section 6.2.8 summarizes consumer beliefs about the health risks of using the candidate product relative to cessation aids.
- Section 6.2.9 summarizes consumer beliefs about the risks of using the product relative to quitting all tobacco use.
- Section 6.2.10 provides a summary of comprehension of the proposed claim and risk perceptions in users and nonusers of tobacco products.

Based on the results of our CCI Study, we conclude that adult tobacco users and non-users (including LA-24 year olds) understand and do not misinterpret the advertising and labeling

with the proposed claim. Adult tobacco users and non-users continue to believe that candidate product use poses risk to health after viewing advertising and labeling with the proposed claim and that using NRTs, quitting tobacco use, or never using tobacco products are less risky choices. The non-MST user subgroups (adult smokers, non-users and former tobacco users) generally have higher perceived levels of risk than current MST users. The single exposure to our proposed claim had no effect on perceptions of the health risk of the candidate product as compared to cigarettes; risk perceptions proved consistent with literature findings in failing to differentiate the substantial difference in risk between the candidate product and cigarettes.

3. Effect on Tobacco Use Behavior Among Current Users

Section 6.3 discusses the potential for exposure to the proposed claim to change tobacco use behaviors among current tobacco consumers.

This section summarizes results from the CCI Study (Section 7.3.2) on changes in behavioral intentions regarding the candidate product after viewing the proposed claim relative to the pre-test, as compared to a control group which viewed an advertisement for the candidate product without the claim.

This section also provides a summary of a clinical study (Appendix 7.3.1-1) comparing the nicotine pharmacokinetics and subjective measures for the candidate product relative to the adult smokers' own brand cigarette and Nicorette[®] polacrilex gum.

- Section 6.3.3 summarizes the likelihood that current tobacco product users will start using the product.
- Section 6.3.4 summarizes the likelihood that tobacco users who adopt the candidate product will switch to or switch back to other higher risk tobacco products.
- Section 6.3.5 summarizes the likelihood of dual use with other tobacco products.
- Section 6.3.6 summarizes the likelihood that users who may have otherwise quit using tobacco products will instead use the product.
- Section 6.3.7 summarizes the likelihood that users will use the product as intended or designed.
- Section 6.3.8 summarizes the evidence regarding abuse potential of the candidate product.

Results from our CCI study show that claim exposure did not result in any significant changes in behavioral intentions to try or use the candidate product. Additionally, the CCI Study results indicated that exposure to the proposed modified risk claim did not adversely alter quitting intentions in AS.

Overall, we expect low likelihood of immediate behavior changes in tobacco product use based on the CCI Study results. We anticipate that the emphasis on “complete switching” and prolonged exposure to marketing information containing the proposed claim will, over time, contribute to more accurate understanding of product risk, adjustment of prior beliefs, and encouragement for ATC to start using the candidate product instead of cigarettes. The abuse

potential of the candidate product is lower than cigarettes and greater than, or similar to, that of NRT products, based on its pharmacokinetic profile and subjective effects measured in our study and the published literature. In sum, we have no indication that the candidate product will encourage widespread dependent use of the product by individuals who were previously non-users or who would have quit smoking.

4. Effect on Tobacco Use Behavior Among Non-users

Section 6.4 summarizes our research demonstrating that exposure to the proposed modified risk claim does not adversely impact behavioral intentions among adult non-users, for whom this product is not intended. This section also summarizes publicly available data on prevalence, use patterns, and factors that influence youth usage of MST products.

Our marketing plan for the proposed claim (Section 4.1) is directed at adult smokers including adult dual users of MST and cigarettes, while limiting reach among unintended audiences. Consistent with this approach, the phrase “IF YOU SMOKE, CONSIDER THIS” is intended to narrow the focus of our claim communication to these audiences. The CCI study (Section 7.3.2) evaluated behavioral intentions among adult former- and never-tobacco product users who viewed an advertisement with the proposed claim (Test condition) compared to those who viewed a product advertisement without the proposed claim (Control condition).

- Section 6.4.2 summarizes the likelihood that consumers who have never used tobacco products, particularly youth and young adults, will initiate use of the tobacco product.
- Section 6.4.3 summarizes the likelihood that nonusers who adopt the tobacco product will switch to other tobacco products that present higher levels of individual health risk.
- Section 6.4.4 summarizes the likelihood that former users of tobacco products will reinitiate use with the tobacco product.

We conclude the following, based on the results of our CCI study in non-users of tobacco products (and also non-users LA-24) that there is low likelihood that former and never users of tobacco products, including young adult (LA-24 year old) non-users, will adopt the candidate product in the presence of advertising and labeling materials with the proposed claim. The CCI Study reflected lack of interest in the candidate product among adult non-users, which was not altered by exposure to the proposed claim.

Additionally, based on our comprehensive review of the published scientific literature and analyses of national survey data, we find no evidence that marketing the candidate product with the proposed claim will have an unintended effect of increasing youth initiation of the product beyond the current rates observed for the category.

We intend to monitor the effect of the claim on any potential changes in use behavior in non-users through a comprehensive postmarket surveillance program.

5. Effect on the Population as a Whole

Section 6.5, demonstrates that introducing the candidate product with the proposed modified risk claim will benefit the population as a whole.

We summarize the findings from our dynamic population model. This model estimates the all-cause mortality in a hypothetical population of never-users of tobacco, including possible transitions into and out of cigarette smoking, MST use, and dual use. This model compares lives saved between a hypothetical “Base Case” and a counterfactual “Master Case” in which the proposed modified risk claim is likely to result in changes in tobacco use behaviors. We derive the transition rates between various tobacco use states in the base-case from U.S. data, including national public health surveys, published scientific literature, and our own survey data. In the modified case, we modify the transition rates between tobacco use states based on the results of the CCI Study, reflecting a future state under market authorization of the proposed modified risk claim.

- Section 6.5.2 describes the ALCS Cohort Model Framework.
- Section 6.5.3 provides the Compartmental Model Overview.
- Section 6.5.4 summarizes the ALCS Single Cohort Model including model validation, assumptions and limitations.
- Section 6.5.5 describes the Multiple Cohort Model.
- Section 6.5.6 delineates our approach towards population model input parameters.
- Section 6.5.7 provides the modeling outcomes.

At the category level, the ALCS Cohort Model results demonstrate a net positive benefit to the U.S. population through both the single-cohort and multi-cohort modeling approaches. The single-cohort modeling approach results in 1,120 additional survivors from a cohort of one million; and 32,856 years of additional life sustained. Similarly, the time-staggered, multi-cohort approach predicts 93,000 additional survivors among the U.S. native-born male population after a follow-up period of 60 years.

To better approximate the net population benefit gained by authorizing marketing of the candidate product with the proposed claim, we scale multi-cohort model results using the candidate product’s current market share, yielding 7,500 additional survivors among the U.S. native-born male population after a follow-up period of 60 years.

Our validated model developed using a published list of modeling best practices and tested using uncertainty and sensitivity analyses indicates that authorization of the proposed modified risk claim for the candidate product yields a net population health benefit.

Summary

Based on Wave 1 of FDA's PATH survey, there are 42.8 million smokers in the U.S. About 6.6 million adults currently use ST, and about 2.3 million adults are using both cigarettes and ST.⁹ Our proposed claim accurately communicates an important risk differential between the candidate product and cigarette smoking – information these adult tobacco users are entitled to receive. Accurately informing consumers about the benefit of complete switching should encourage those who will continue using tobacco products to make the informed decision to exclusively use the candidate product instead of smoking cigarettes.

ST products, including the candidate product, have been available in the U.S. market for nearly two centuries and a substantial body of published epidemiological evidence describes the health effects of ST products as used in the U.S.

This evidence demonstrates that, while not risk-free, these products offer a substantial difference in lung cancer mortality risk compared to cigarette smoking. Current scientific data support that adult smokers who stop smoking and completely switch to the candidate product will reduce their mortality risk from lung cancer. We foresee minimal unintended consequences resulting from our proposed claim and expect an overall net benefit to the population.

⁹ Source: Based on ALCS analysis of PATH Wave 1 data Sep 12, 2013 – Dec 14, 2014

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